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Extent of Early ST Segment Elevation Resolution: A Strong Predictor of Outcome in Patients With Acute Myocardial Infarction and a Sensitive Measure to Compare Thrombolytic Regimens

A Substudy of the International Joint Efficacy Comparison of Thrombolytics (INJECT) Trial

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Objectives. **This study was undertaken to assess prospectively the prognostic power of early ST segment elevation resolution in a large cohort of patients with myocardial infarction and to test the value of differences in ST segment resolution as a surrogate end point.**

Background. **Previous studies revealed that the use of two cutoff points for three groups of ST segment resolution within 3 h after the start of thrombolysis is most effective in predicting outcome.**

Methods. **The International Joint Efficacy Comparison of Thrombolytics (INJECT) trial compared mortality in 6,010 patients randomized to receive either reteplase or streptokinase. The 1,909 German patients form the basis of this substudy. The three groups of ST segment resolution were defined as complete (≥70%), partial (70% to 30%) and no resolution (<30% to ≥0%).**

Results. **In 1,398 patients presenting ≤6 h from onset of acute myocardial infarction, the 35-day mortality rate for complete, partial and no ST segment resolution was 2.5%, 4.3% and 17.5%, respectively ($p < 0.0001$). Peak creatine kinase levels (fraction of normal) were 9.8, 13.4 and 14.0, respectively ($p < 0.0001$). When baseline characteristics were included, ST segment resolution was the most powerful independent predictor of 35-day mortality. The proportion of patients with complete ST segment resolution was larger, and that with no ST segment resolution smaller, with reteplase than with streptokinase ($p = 0.006$).**

Conclusions. **No ST segment resolution, indicating failed thrombolysis, predicts very high early mortality, whereas complete resolution is associated with a small infarct area and low mortality. Partial ST segment resolution also predicts larger infarct areas, but early mortality is relatively low. Different extents of ST segment resolution may serve as a sensitive surrogate end point in clinical trials.**

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In patients with evolving myocardial infarction, an early prognostic indicator that is easy to use in all patients is highly desirable. In only a few studies has resolution of electrocardiographic (ECG) ST segment elevation been tested as a prognostic indicator (1–3), in contrast to coronary reperfusion predicted by ST segment changes, which has been investigated by numerous investigators (4). In prior studies that predicted outcome for ST segment elevation resolution, one cutoff point was applied. As an improvement, we used two cutoff points, which were first applied in two smaller prospective studies (4,5). The validity of the model was tested in a retrospective analysis in 1,516 patients from the Intravenous Streptokinase in Acute Myocardial Infarction (ISAM) study (6) data base, which provided a large, well characterized patient group for whom multivariate analyses could be performed to identify independent determinants of mortality (7). These studies showed that cutoff points of ST segment resolution ≥70% and <30% are most effective for predicting infarct size, left ventricular function and early as well as long-term survival.

In the ISAM study (6), streptokinase infusion showed only a nonsignificant trend in reduction of mortality. The predictive power of the ST segment resolution was the same regardless of whether patients had received streptokinase or placebo infusion (7). However, there was a significant difference in the extent of ST segment resolution in favor of streptokinase ($p < 0.0001$).

We next conducted a substudy in conjunction with the International Joint Efficacy Comparison of Thrombolytics (INJECT) trial 1) to assess prospectively the prognostic power of the ECG markers in a large cohort of patients with acute myocardial infarction; and 2) to test prospectively the value of

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Table 1. Reasons for Exclusion of 233 Patients From Evaluation of Predictive Power of ST Segment Elevation Resolution*

	No. (%) of Pts
Died before 3-h ECG	16 (0.8)
No study drug	27 (1.4)
No ST segment elevation	64 (3.4)
No 3-h ECG	92 (4.8)
Not evaluable	7 (0.4)
Outside time window	85 (4.5)
QRS ≥0.12 ms	38 (2.0)
BBB, no MI	16 (0.9)
BBB, no ST ↑	8 (0.4)
WPW syndrome	2 (0.1)
Pacemaker	4 (0.2)
Ideoventricular rhythm	8 (0.4)
Total	233 (12)

*Patients (Pts) with events of different types appear more than once in the column but only once in the total. BBB = bundle branch block; ECG = electrocardiogram; MI = myocardial infarction; no ST ↑ = absence of ischemic ST segment elevation on prerandomization ECG; WPW = Wolff-Parkinson-White.

differences in ST segment elevation resolution as a measure of the differential effectiveness of thrombolytic regimens.

Methods

The INJECT trial was a multicenter, double-blind, randomized trial that compared reteplase, 10 plus 10-million unit double-bolus administration, with streptokinase in patients admitted within 12 h from the onset of acute myocardial infarction. Details of the rationale, design and main results of the study are available in the original report (8). Between August 1993 and September 1994, 6,010 patients were recruited from nine European countries. Patients of any age were eligible for randomization if they had no clear contraindications to thrombolytic therapy and had an ST segment elevation ≥0.1 mV in at least two limb leads or ≥0.2 mV in two contiguous precordial ECG leads or the presence of bundle branch block.

Study patients. All 1,909 patients recruited for the INJECT trial in Germany were considered for analysis. A 12-lead ECG was recorded before and 3 h after randomization, and the ST segment deviation was evaluated centrally, independent of and blinded to the other study data or results.

For various reasons (Table 1), 233 patients (46 of whom were randomized >6 h from onset of acute myocardial infarction) had to be excluded from the evaluation of the predictive power of ST segment resolution. Sixty-four patients (3.4%) did not show the required amount of ST segment elevation at baseline (most did not develop a definite myocardial infarction). In 92 patients (4.8%), a 3-h ECG was not available or was recorded outside the 3-h time window. A broad QRS complex was present in 38 patients (2%). In 16 of 24 patients who had a bundle branch block but no ischemic ST segment elevations, a suspected acute myocardial infarction was not confirmed. (Patients with bundle branch block and ischemic ST segment elevation are included in the analysis.) Of the 233 excluded patients, 34 died within 35 days (18 had received reteplase and 16 streptokinase); 16 of them died early, that is, before the 3-h ECG could be recorded.

Because it was expected that the model of ST segment resolution might not be valid >6 h after symptom onset, evaluation of patients randomized >6 h from symptom onset had been prespecified in the study protocol. Indeed, in the 278 evaluable patients presenting >6 to 12 h, the sum of ST segment elevation in the prerandomization ECG was significantly lower than that in patients randomized earlier (anterior myocardial infarction 1.25 vs. 1.63 mV; inferior myocardial infarction 0.65 vs. 0.89 mV, both $p < 0.0001$). Many patients presenting later probably already had had a spontaneous decline in their initial ST segment elevation. Therefore, and to be consistent with previous studies (4,5,7), only the 1,398 evaluable patients randomized ≤6 h from symptom onset form the basis of this report.

Electrocardiographic analysis. The sum of ST segment elevation was measured with lens-intensified calipers to the nearest 0.025 mV, 20 ms after the end of the QRS complex from leads I, aVL and V_1 to V_6 for anterior myocardial infarction and leads II, III, aVF, V_5 and V_6 for inferior myocardial infarction (7). Patients with bundle branch block who had clear ischemic ST segment elevations were included in this analysis. In addition, subgroups of patients who had a reciprocal ST segment depression ≥0.1 mV were also evaluated. For the total ST segment deviation (no bundle branch block in this group) the sum of ST segment depression in leads II, III and aVF for anterior and that in leads V_1 to V_4 for inferior myocardial infarction were added (9). The extent of epicardial injury was also quantified by counting the number of leads with ST segment elevation ≥0.1 mV (10).

Prognostic ST segment resolution groups. Consistent with the previous studies (4,7), two cutoff points of ST segment resolution within 3 h after start of thrombolysis were applied. *Complete resolution* was defined as resolution of the initial sum of ST segment elevation (or total deviation) ≥70%. *Partial resolution* was defined as ST segment resolution <70% to 30%. *No resolution* was defined as ST segment resolution <30% to ≥0%. For the 3-h ECG recording, a time window of 2 to 4 h after initiation of thrombolytic therapy was allowed; 95.5% of the ECGs were recorded within this time span (88.5% between 2.5 and 3.5 h).

Enzyme analysis. Peak creatine kinase (CK) isoenzyme serum activity was measured in the participating hospitals and is expressed as fraction of the upper normal limit for the different methods used. To depict the continuous relation between peak CK activity and ST segment resolution, moving averages of length 201 were used with ST segment resolution arranged in descending order (Fig. 1).

Statistical analysis. For univariate analyses only nonparametric methods were applied. Comparisons between the two groups were performed using the Mann-Whitney *U* test for continuous variables and Fisher exact test for dichotomous

Figure 1. Peak creatine kinase (CK) values (fraction of the upper normal limit) in relation to sum (Σ) of ST segment elevation resolution continuously drawn by moving averages from 100% resolution to 0% resolution 3 h after the start of thrombolytic therapy. The ST segment resolution cutoff points of 70% and 30% are marked.

variables (e.g., mortality). Simultaneous comparisons for more than two groups were performed using the Kruskal-Wallis test.

The multivariate analysis consisted of a stepwise logistic regression for outcome at 35 days. In addition to the differences between the indicator variables of the partial and no-ST segment resolution groups to the complete resolution group, 12 baseline variables were offered as covariates: 1) age (taken as a continuous variable, unit 10 years); 2) female gender; 3) ex-smoker or nonsmoker; 4) history of heart failure; 5) previous myocardial infarction; 6) diabetes mellitus; 7) history of angina pectoris; 8) anterior myocardial infarction; 9) acute heart failure; 10) Killip class >I; 11) large sum of ST segment elevation on the initial ECG (>1.2 mV for anterior, >0.6 mV for inferior myocardial infarction); and 12) treatment with reteplase.

Logistic regression was performed using the procedure "LOGISTIC REGRESSION" of SPSS for Windows, Version 5.0.2, choosing the forward-stepping selection method with ML estimates and the default criteria offered by SPSS. The indicator variables of the ST segment resolution contrasts were offered to the selection process as an entity. The odds ratios, confidence intervals and p values of the final model (i.e., adjusted for all other significant covariates) are reported.

Results

Study patients. The clinical characteristics of the 1,398 study patients are presented in Table 2. The group with no ST segment resolution had a higher prevalence of several adverse baseline characteristics. Distribution of infarct location was virtually identical, as in the previous study (7), that is, in the group with complete ST segment resolution, ~67% of patients had an inferior myocardial infarction and ~33% had an anterior myocardial infarction; in the no-resolution group, these findings were reversed.

The severity of ischemia, as assessed by the sum of ST segment elevation in the prerandomization ECG, and the extent of epicardial injury, as quantified by the number of leads with ST segment elevation ≥0.1 mV, were slightly lower in patients with no ST segment resolution than in those with partial and complete ST segment resolution.

Table 2. Clinical Characteristics of 1,398 Patients According to ST Segment Elevation Resolution 3 h After Start of Thrombolytic Therapy

	ST Segment Elevation Resolution at 3 h			
	Complete (n = 682 [49%])	Partial (n = 418 [30%])	No (n = 298 [21%])	p Value
Mean age (yr)	60.9	61.6	62.8	0.07
≥65	39%	42%	46%	0.08
Female	24%	26%	27%	NS
History				
Previous MI	12%	12%	15%	NS
Heart failure	5%	6%	9%	0.05
Diabetes	10%	16%	22%	< 0.0001
Angina pectoris	25%	24%	30%	NS
In-hospital event				
Anterior MI	33%	62%	58%	< 0.0001
BBB	2.9%	5.7%	6.7%	0.01
Killip class >I	10%	14%	23%	< 0.0001
ΣST↑ (mV)*				
Anterior MI	1.72 ± 1.2	1.58 ± 0.8	1.40 ± 0.9	< 0.01
Inferior MI	0.89 ± 0.6	0.86 ± 0.5	0.81 ± 0.5	NS
No. of leads with ST↑ ≥0.1 mV*				
Anterior MI	4.7 ± 1.8	4.8 ± 1.4	4.6 ± 1.5	NS
Inferior MI	3.4 ± 1.1	3.4 ± 1.0	3.1 ± 1.2	0.02

*Mean value ± SD. ΣST↑ = sum of ST segment elevation on the prerandomization electrocardiogram; other abbreviations as in Table 1.

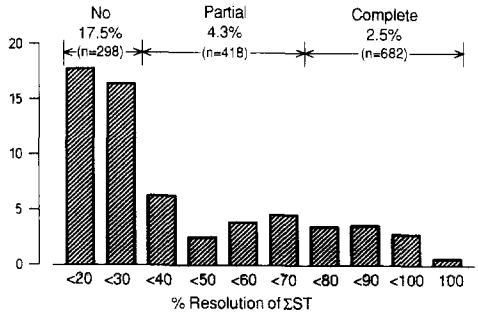

Figure 2. Thirty-five day mortality rates by percent sum (Σ) of ST segment resolution in multiple steps. The rationale for applying a cutoff point of 70% is the development of larger infarct areas in patients with partial ST segment resolution associated with an increasing mortality risk over the long term for anterior myocardial infarction (7). $p < 0.0001$ for mortality rate differences for complete, partial or no ST segment resolution.

Table 4. Causes of Death According to Complete, Partial or No ST Segment Elevation Resolution

	No. of Pts With ST Segment Resolution at 3 h			
	Complete (n = 682)	Partial (n = 418)	No (n = 298)	p Value
Cardiac deaths				
Cardiogenic shock	5	8	17	< 0.0001
Cardiac rupture	1	1	9	< 0.0001
Recurrent MI	1	0	5	< 0.001
Arrhythmia	2	1	0	NS
Other	4	7	20	< 0.0001
Total	13	17	51	< 0.0001
Noncardac deaths				
Stroke	2	1	1	NS
Other	2	0	0	NS
Total deaths	17	18	52	< 0.0001

Abbreviations as in Table 1.

Infarct size and mortality according to complete, partial or no ST segment resolution. Peak CK activity was significantly lower in patients with complete resolution (9.8) than in those with partial (13.4) or no resolution (14.0) ($p < 0.0001$). Peak CK activity gradually increased from 7.1 (fraction of the upper normal limit) at 100% ST segment resolution to 13.3 at 70% (range for complete resolution) and leveled off thereafter at ~13.4 until 30% (partial) and ~14 from <30% to ≥0% ST segment resolution (range for no ST segment resolution) (see Fig. 1).

The 35-day mortality rates by percentage of ST segment resolution in multiple steps are shown in Figure 2. Patients with complete ST segment resolution have a very low mortality risk of only 2.5%; they comprise nearly one-half of all study patients (34% of anterior and 62% of inferior myocardial infarction patients). In contrast, no ST segment resolution, as observed in 21% of patients (26% anterior, 17% inferior infarction), was associated with an exceptionally unfavorable outcome (17.5% mortality rate). In Table 3, the mortality rates of the subgroups with anterior or inferior myocardial infarction (bundle branch block excluded) and for patients with bundle branch block are presented. Mortality is similarly low, with complete ST segment resolution in both infarct locations. High mortality with no ST segment resolution is more common in patients with anterior myocardial infarction, especially in the subset of those who had reciprocal ST segment depression on their initial ECG. Mortality is exceptionally high in patients with bundle branch block and no resolution of the initial ischemic ST segment elevation.

Causes of death are given in Table 4. There was no difference in the incidence of arrhythmia deaths between the three resolution groups; however, all other causes of cardiac death were more often associated with no ST segment resolution.

Prognostic impact of extent of ST segment resolution in risk subsets. Various cardiac event rates subdivided by the three resolution groups are presented in Table 5. Malignant tachyarrhythmias, cardiogenic shock and heart failure were observed more often with no ST segment resolution.

The 35-day mortality rate by clinical variables, identified or known (7) to be independent predictors of survival, are shown in Table 6. For each risk subset, mortality was low (at least relatively so) with complete ST segment resolution but extremely high with no ST segment resolution. Of special note is the mortality rate of 62% in patients with recurrent myocardial infarction, who had had no ST segment resolution, and the relatively low mortality rate of 33% in patients with cardiogenic shock, whose initial ST segment elevation completely resolved 3 h after the start of thrombolysis.

Table 3. Thirty-Five Day Mortality Rate According to Complete, Partial or No ST Segment Resolution in Subgroups of 1,398 Patients Presenting ≤6 h From Symptom Onset

	Mortality Rate (%) by ST Segment Resolution at 3 h			
	Complete	Partial	No	p Value
Anterior MI	1.9 (4/212)	2.9 (7/242)	17.2 (27/157)	< 0.0001
ST segment depression	1.6 (2/122)	3.4 (4/117)	24.2 (16/66)	< 0.0001
Inferior MI	2.7 (12/450)	5.9 (9/152)	14.0 (17/121)	< 0.0001
ST segment depression	2.9 (9/314)	5.1 (5/98)	14.5 (11/76)	< 0.0001
BBB	5.0 (1/20)	8.3 (2/24)	40.0 (8/20)	< 0.005

Numbers in parentheses are number of patients. ST segment depression = resolution of total ST segment deviation in the subsets of patients who had reciprocal ST segment depression on their initial electrocardiogram; other abbreviations as in Table 1.

Table 5. Clinical Event Rate* According to Complete, Partial or No ST Segment Elevation Resolution

	Total No. of Pts With Events	Event Rate (%) by ST Segment Elevation Resolution at 3 h			
		Complete	Partial	No	p Value
Recurrent MI	90	6.2 (42)	5.3 (22)	8.7 (26)	NS
AP/ischemia	171	13 (87)	10 (41)	14 (43)	NS
PTCA/CABG	329	27 (186)	20 (83)	20 (60)	< 0.01
VF/VT	222	13 (89)	15 (63)	24 (70)	< 0.0005
Killip class >I	192	10 (67)	14 (57)	23 (68)	< 0.0001
Heart failure	265	13 (89)	20 (81)	32 (95)	< 0.0001
Cardiogenic shock	84	2.6 (18)	3.8 (16)	17 (50)	< 0.0001

*Present after enrollment. Numbers in parentheses are number of patients. AP = angina pectoris; CABG = coronary artery bypass graft surgery; PTCA = percutaneous transluminal coronary angioplasty; VF = ventricular fibrillation; VT = sustained ventricular tachycardia; other abbreviations as in Table 1.

Multivariate logistic regression analysis revealed five covariates that were independent predictors of 35-day mortality (Table 7). The entity of the ST segment resolution groups is the most powerful, with an odds ratio of 6.9 for no versus complete ST segment resolution.

Comparison of reteplase and streptokinase. Of all 1,585 patients randomized ≤6 h from symptom onset, 111 (7%) died by day 35; 49 (6.3%) of 782 had received reteplase, and 62 (7.7%) of 803 had received streptokinase. The mortality rate in the patients evaluated was 87 (6.2%) of 1,398: reteplase in 36 (5.2%) of 692 and streptokinase 51 (7.2%) of 706. None of the mortality differences was statistically significant ($p = 0.26$ for all patients, and $p = 0.12$ for all patients evaluated). However, there was a significant difference in the extent of ST segment elevation resolution ($p = 0.006$). More patients had complete, and less had no, ST segment resolution in the reteplase group (Table 8). These differences remained significant even when patients who were randomized >6 h from symptom onset were included into the analysis ($p = 0.02$).

Discussion

Ideally, an early prognostic indicator in patients with acute myocardial infarction should be simple, quick, noninvasive and easy to use in all patients. An assessment by ECG criteria would fulfill all of these claims. Early ST segment elevation resolution has been tested in a few studies by applying one cutoff point of ST segment resolution. Saran et al. (1) used a cutoff point <30% ST segment resolution at 3 h in 45 patients. Barbash et al. (2) used 50% reduction after 1 h in 286 patients, and Mauri et al. (3) used 50% reduction 4 h after the start of thrombolysis in a Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI 2)–derived analysis of 7,426 patients. Consistently, a lesser degree of ST segment resolution was associated with a significantly worse outcome. However, these studies had the limitation that the groups with greater ST segment resolution included too many patients with still severely depressed left ventricular function, and, vice versa, the groups with

Table 6. Thirty-Five Day Mortality Rate by Risk Group According to Complete, Partial or No ST Segment Elevation Resolution

	No. of Pts.	Mortality Rate (%) by ST Segment Elevation Resolution at 3 h			
		Complete	Partial	No	p Value
<65 yr old	21/821	0	2	10	< 0.0001
≥65 yr old	66/577	6	7	26	< 0.0001
Male	49/1,045	2	3	14	< 0.0001
Female	38/353	5	7	28	< 0.0001
Clinical event*					
Recurrent MI	25/90	12	18	62	< 0.0001
Killip class >I	30/192	4	7	34	< 0.0001
Heart failure	39/265	3	11	28	< 0.0001
Cardiogenic shock	56/84	33	63	80	< 0.005
History					
Previous MI	18/171	3	17	18	< 0.01
Diabetes	26/203	4	7	27	< 0.0001
Angina pectoris	38/362	5	10	22	< 0.0001
Heart failure	20/85	14	17	41	< 0.05

*Present after enrollment. Abbreviations as in Table 1.

Table 7. Multivariate Analysis for Prediction of 35-Day Mortality Based on ST Segment Resolution Groups and 12 Other Variables in 1,398 Patients Presenting ≤6 h After Symptom Onset

Variable	Selected at Step	OR (95% CI)	p Value
ST segment resolution	1		< 0.0001
Partial vs. complete		1.6 (0.8–3.3)	NS
No vs. complete		6.9 (3.8–12.5)	< 0.0001
Age (10-yr steps)	2	2.2 (1.7–2.8)	< 0.0001
History of heart failure	3	2.5 (1.3–4.7)	0.006
Acute heart failure	4	2.1 (1.3–3.5)	0.004
History of angina	5	1.7 (1.0–2.7)	0.04

CI = confidence interval; OR = odds ratio.

lesser ST segment resolution included patients with a relatively favorable outcome.

We proposed to solve this problem by applying two cutoff points, which created three groups of ST segment resolution with complete (≥70%), partial (<70% to ≥30%) or no (<30%) ST segment resolution (4,5,7). The present substudy of the INJECT trial, using a large and well defined patient cohort, confirms the strong prognostic power of the simple ECG marker available 3 h after the start of thrombolytic therapy. To be consistent with previous studies (4,7), 278 patients presenting >6 h after symptom onset were excluded from the present analysis, although the results remain virtually the same when all randomized patients are analyzed. Because patients presenting later had already had a spontaneous decline in their initial ST segment elevation, the predictive power of (further) ST segment reduction may be limited. However, complete ST segment resolution in these patients was still associated with low mortality (none of 71 patients died), although there was no mortality difference in patients with partial (10.5%) or no ST segment resolution (9.1%). Therefore, whether the ECG marker is also useful in patients presenting later is unclear.

Prognostic value of either complete or no ST segment resolution. Complete ST segment resolution in ~50% of all patients predicts an excellent survival. None of 419 patients <65 years old died by 35 days. In patients with potentially larger infarctions, as evidenced by anterior infarct location, bundle branch block or additional reciprocal ST segment depression on the initial ECG, mortality differences between complete or no ST segment resolution are more distinct. In all patient groups known to be generally at higher risk of dying, complete ST segment resolution still signifies a favorable outcome. A lower incidence of adverse cardiac events (Tables 4 and 5) and an improved survival (Table 6) in patients exhibiting ≥70% ST segment resolution within 3 h after initiation of thrombolytic therapy are consistent with improved early reperfusion and limitation of infarct size. In contrast, lack of ST segment resolution, as observed in 17% of reteplase-treated and 25% of streptokinase-treated patients, indicating persistent ischemia and probably failed thrombolysis, is associated with an exceptionally high mortality risk.

At the cutoff point of <30% ST segment resolution, there is an abrupt, massive increase in early mortality (Fig. 2) similar to that observed in the ISAM study–derived analysis (7). This finding is at variance to the GISSI-2–derived data, which show a more gradual increase in mortality rate, from 3.1% with 100% ST segment resolution to 11.1% with <10% ST segment resolution (3). However, 41% of all GISSI study patients were excluded from the evaluation. The 30-day mortality rate was 4.8% in the evaluated group compared with 9.4% in the entire study population. Thus, the secondary analysis is limited to a relatively low risk population. Furthermore, to demonstrate a direct relation between mortality and the percent reduction in ST segment elevation, apparently data for 6-mo mortality are provided (stated as in-hospital mortality in the paper). Because mortality "catches up" over the long term in patients with partial ST segment resolution (7), an early 30% ST segment resolution gap may already have somewhat smoothed off at 6 mo.

Lack of ST segment resolution in the present study is associated with a 35-day mortality rate of 17.5%, whereas with ≥30% ST segment resolution the 35-day mortality rate was 3.2% (2.5% with complete, 4.3% with partial ST segment resolution). As in the ISAM study–derived analysis (7), lack of ST segment resolution within 3 h after the start of thrombolysis was the most powerful independent predictor of early mortality. This prognostic power may even be greater than that of the patency status of the infarct-related artery as assessed angiographically at 90 min after the start of thrombolysis. A meta-analysis of the major published trials reporting the

Table 8. Percent of Patients With Complete, Partial or No ST Segment Elevation Resolution Allocated to Receive Reteplase or Streptokinase

	All Pts		Anterior MI		Inferior MI	
	RP (n = 692)	SK (n = 706)	RP (n = 318)	SK (n = 337)	RP (n = 374)	SK (n = 369)
ST segment resolution (no. of pts)						
Complete	51	46	36	33	65	59
Partial	31	29	43	37	22	21
No	17	25	22	31	14	20
p value	0.006		0.08		0.04	

RP = reteplase; SK = streptokinase; other abbreviations as in Table 1.

relation between mortality and patency status of the infarct-related artery in 3,960 patients (11) revealed a mortality rate of 3.8% for complete vessel patency, whereas with an occluded artery or sluggish flow only (Thrombolysis in Myocardial Infarction [TIMI] grade 2 flow), the mortality rate was 8.9% and 6.7%, respectively. It appears that different extents of ST segment resolution within 3 h after the start of thrombolysis contain more comprehensive, prognostically important information than does the patency status of the infarct-related artery alone (4). Persistent ischemia at 3 h identifies a high risk group more clearly than a "snapshot" view of coronary patency at 90 min, which does not allow differentiation between patients with improving, stable or deteriorating infarct vessel patency (11).

Partial ST segment resolution. Although <30% ST segment resolution predicts high early mortality, <70% ST segment resolution predicts larger infarct areas. Peak CK activity as used in the present study is not the best index of infarct size because this measure is known to be further elevated by effective thrombolysis (6). However, when more precise measures, such as infarct size calculated from CK-MB release or development of Q waves, and left ventricular function assessed by cineangiography 1 mo after myocardial infarction were used, 70% ST segment resolution was also an excellent cutoff point for predicting infarct size (7).

According to studies (1,4,12–14) comparing angiographic vessel patency and ST segment changes, even only partial ST segment resolution (between ≥30% and <70%) indicates reperfusion in most patients. However, in these studies TIMI grade 2 and 3 flow has been considered patent. It is now well established that TIMI grade 2 flow should be considered occluded and designated as reperfusion failure rather than success (11). Krucoff et al. (15) evaluated patency status by means of a newer technique of ST segment recovery analysis during continuous 12-lead ECG. They found that ST segment changes probably comparable to our partial ST segment resolution may occur with TIMI grade 2 flow as well as with collateralized occlusion. Other mechanisms involved in the development of larger infarct areas identifiable by partial ST segment resolution may include abrupt reopening of an initially persistent complete occlusion of a major coronary branch (16,17) and relatively late reperfusion (4). Whatever the mechanisms are, the relatively low early mortality indicates that patients with partial ST segment resolution may still have benefited from thrombolysis. Even small changes in left ventricular function may be of particular importance in patients with poor left ventricles to begin with. However, some subsets, like those with cardiogenic shock or a history of previous myocardial infarction, may require complete ST segment resolution to predict improved survival (Table 6).

Comparison of reteplase and streptokinase. Reteplase is a recombinant mutant of tissue-type plasminogen activator (t-PA) with a longer half-life than alteplase (8). It provides significantly higher 90-min patency rates than the traditional 3-h infusion of alteplase (18–20). Early TIMI grade 3 flow is comparable or even superior (21) to that obtained by the accelerated t-PA regimen introduced by Neuhaus et al. (22). More rapid and complete restoration of coronary flow through the infarct-related artery is believed to be the principal mechanism by which accelerated t-PA improves survival (23). Today, the prognostic significance of early TIMI grade 3 flow is generally accepted. However, to achieve a statistically significant 14% relative reduction in mortality with accelerated t-PA, compared with streptokinase, >40,000 patients were randomized in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial (23). By analogy, to prove directly a mortality benefit for reteplase compared with streptokinase, a trial on the GUSTO scale would be needed (8). Because it is obviously impossible to conduct a megatrial to prove the benefit of each new thrombolytic agent, each new treatment regimen or the advantage of antithrombotic or other adjunctive treatments, there is clearly the need for a more practical means of evaluation that enables us to compare innovative thrombolytic regimens in much smaller trials (8,24).

There is a very close correlation between cardiac mortality and extent of ST segment elevation resolution in patients with evolving myocardial infarction. Therefore, a larger extent of ST segment resolution may serve as a surrogate for improved survival. In trials not primarily designed to assess mortality differences, different extents of ST segment resolution may provide a sensitive measure of differential clinical benefits. The much larger number of ST segment resolution end points can provide statistically significant results with much less resources than would be needed for differences in mortality. As expected, the statistical power for differences in ST segment resolution between streptokinase and placebo was stronger (7) than that between reteplase and streptokinase. However, a clear benefit for reteplase still exists. Taking into account the satisfactory safety profile observed for reteplase (8), higher early vessel patency and better ST segment resolution may also serve a surrogate end points, suggesting that reteplase is superior to streptokinase.

Clinical implications. Patients with complete ST segment resolution may be scheduled for early discharge without routine angiography. Only patients with suspected extensive coronary artery disease and those with recurrent ischemia or stress test results indicative of ischemia should be considered for angiography and revascularization maneuvers. In patients with lack of ST segment resolution, identifying those patients who have a poor prognosis without reperfusion and patients in whom reperfusion might be expected to provide substantial benefit, early angiography and revascularization may be indicated (25). Patients with partial ST segment resolution, in whom the risk prediction is less conclusive, may require a more extensive diagnostic assessment of their cardiac status and therapeutical approach. In the ISAM study–derived analysis (7), over the long term, patients with anterior myocardial infarction and partial ST segment resolution carried an increasing mortality risk.

Study limitations. There are some factual or putative limitations of the present study.

1. Thirteen percent of patients randomized within ≤6 h from symptom onset were excluded from the evaluation of the prognostic power of ST segment resolution within 3 h after the start of thrombolysis. Assuming the worst case scenario, that is, that all patients who survived the first 3 h would have had complete ST segment elevation resolution, the mortality rate at 35 days would account for 3.3% instead of the 2.5% evaluated. Therefore, the exclusion of patients virtually did not affect the results.

2. The time window for the 3-h ECG was 2 to 4 h, which may appear rather large. We also performed all calculations applying a time window of 2.5 to 3.5 h. The results are virtually the same, that is, inclusion of the 93 patients (four died at day 35) who were in the wider time window did not affect the results. These findings, indicating that a strict time of 3 h after the start of thrombolysis is not mandatory for recording the "3-h ECG," are noteworthy and an advantage rather than a disadvantage of the model.

3. Exact measurement of the sum of ST segment elevations is cumbersome and would affect the simplicity of the model. However, in most cases exact measurements are not needed because they can easily be identified by visual comparison of the two ECG tracings as having either almost complete or almost no ST segment elevation resolution. In addition, ST segment resolution measured only in the one lead with initially high ST segment elevation closely correlates with the sum of ST segment resolution ($r = 0.93$).

Conclusions. The amount of ST segment resolution within 3 h after the start of thrombolytic therapy conveys very useful information about the outcome in patients with acute myocardial infarction of ≤6 h duration and may also serve as a sensitive surrogate end point in clinical trials. The predictive power of this simple, noninvasive, early marker of prognosis, which is easy to use in all patients who survive 3 h after admission, is extraordinarily strong and helpful for timely triage of patients to appropriate therapeutic interventions.

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